Remarks

The pending claims were all rejected under § 112 first paragraph. Claim 38 was further rejected under § 112 second paragraph as missing essential process steps. Claims, other than claims 41, 50, 57, and 58, were rejected under § 102. In view of the amendment above, and remarks below, reconsideration is respectfully requested.

§ 112, First Paragraph Rejections

The Office Action asserted that the application did not provide sufficient detail to enable the skilled person to understand and carry out the invention across the scope of the claims without undue experimentation. The Office Action has further asserted that there was insufficient written description to confirm that the applicant had possession of the invention.

To better address these concerns, claim 38 is now amended to specify that the solution is in a state such that the protein is at least partially denatured, but self-association of the protein can still occur. This is the core requirement for formation of an amyloid fibril to occur. In this regard, the protein must be denatured sufficiently for its conformation to change, and (in spite of this conformational change) the protein molecule must still be able to associate with other like molecules in an amyloid fibril. This concept finds support in, among other places, paragraph [0025] of the original application.

As further enabled in the original application, a balance between denaturing and self-association may be achieved simply by varying a few basic conditions such as protein concentration, ionic strength and pH. Denaturing agents such as alcohols and urea may also be used to this effect. Conditions should be strong enough to allow a degree of conformational change, e.g. unfolding of a globular protein, and also weak enough that the hydrogen bonds stabilizing the

protein structure are retained and bonds between protein molecules may still be achieved.

The particular balance will vary somewhat with different proteins, but a suitable balance may be easily found by the skilled person having access to the original application, and a standard level of skill in the art, simply by altering the conditions of the solution, for example as indicated in claims 55 and 60.

For example, the present application provides guidance in claim 60 regarding ranges for varying temperature, pH and peptide concentration. Also, specific examples are given.

The application also goes on to teach a number of further changes that can be made, for example the use of specific denaturing agents. The skilled person would be able to select factors for variation depending on the particular proteins selected, and the basis of the particular experiment being carried out. Such experimentation would be routine, once one has access to the original application. The skilled reader would learn from the general teachings of the original application which conditions could be varied, and he/she could then easily adjust any of these until a suitable balance is achieved, allowing the formation of amyloid fibrils.

The skilled person would be able to monitor the presence of such aggregation during these experiments using widely known techniques, such as measuring the turbidity of the solution, or assessing the presence of aggregates that are able to bind characteristic dyes such as Congo Red. Suitable methods for assessing such amyloid fibril formation are also set out in the examples of the original application.

Only routine experimentation in this way would be needed to find conditions under which a selected peptide will form amyloid fibrils. On the basis of the teaching contained in the present application, together with a background knowledge of other factors that can be varied or added which skilled

practitioners already have to achieve particular functions, the skilled person could easily conduct simple experiments to find suitable conditions for fibril formation from a selected peptide.

Crude aggregation and fibril formation should be easily achieved, and once the basic conditions have been determined it would be straightforward to optimize the conditions. Indeed, it can be envisaged that a large number of such tests could be carried out simultaneously by simply setting up a variety of solutions of different formulations and assessing the presence of fibrils after a set time period.

There would be no undue burden here and no complex or arduous experiments would be required. It was well within the knowledge and ability of the skilled person at the priority date to generate protein solutions under a variety of mildly denaturing conditions as required by the claims, and to assess using routine and simple methods which of these allowed the formation of amyloid fibrils. Of course, before the present invention, the skilled person would have had no reason to try these straightforward experiments.

Apart from the arguments with respect to the broader claims, Applicants would also call the examiner's attention to claims 55, 60 and 61 in particular. These most preferred forms are clearly enabled.

With respect to the written description issue, the amended language was within the possession of the inventor as confirmed at paragraph [0025] containing the following sentence, "In the case of naturally occurring proteins conditions are typically chosen to denature at least partially the protein whilst retaining conditions in which self-association can occur.".

§ 112, Second Paragraph Rejection

Claim 38 was further rejected for omitting an essential step. The above amendment is believed to directly address this concern.

§ 102 - Jarrett et al. Reference

It is believed that the cited Jarrett et al. reference does not teach the amended claim language, regardless of how it was previously applied as against the earlier versions of the claims prior to this amendment.

In any event, it should be noted that amyloid fibrils formed by β protein are characteristic of Alzheimer's disease. The β amyloid protein is derived from the putative transmembrane region of the precursor protein βAPP (see page 12345, column 1, second sentence of Jarrett). Thus, although this sequence would normally (in βAPP) be expected in a transmembrane location, it may also be found *in vivo* in the form of extracellular amyloid deposits.

A common assumption at the time Jarrett et al. was published was that because only a small number of proteins were known to form such amyloid fibrils *in vivo*, this ability must derive somehow from their sequence or secondary conformation. Jarrett et al. thus aimed to identify the sequence or structural characteristics of β protein which conferred this amyloid-forming ability.

As explained at the last sentence of the first column, page 12345, "The premise of the studies described herein is that the C-terminus of the β protein contains a primary and/or secondary structural motif which may occur in other amyloidogenic proteins.".

Jarrett et al. did not report that the ability to form amyloid fibrils was common to all proteins, and this is not suggested anywhere in this document. Rather, Jarrett et al. aimed to identify other "amyloidogenic proteins" based on the sequence similarity with β protein.

Jarrett et al. approached this task by setting out a hypothetical consensus sequence based on the part of the β protein sequence believed to be involved in amyloid fibril formation (see page 12345, column 2 and page 12346, "Protein Sequence Search"). On this basis Jarrett et al. selected a peptide corresponding to residues 28-44 of the OsmB protein. This peptide fragment was selected solely on the basis of its similarity to β protein, and indeed, could be considered simply a variant of the β protein sequence.

The peptide used was not OsmB itself. Rather, the sequence comparison was used to find regions of sequence similarity to β protein lying within other proteins. Although the peptide used was identified because of its existence within the OsmB sequence, it is actually an artificially generated peptide, and in any event not a naturally occurring peptide as required by new claim 61. Jarrett et al. thus simply reports the formation of amyloid fibrils using an artificially generated variant of β protein, not β protein.

Further, the Office Action has suggested that OsmB cannot form "naturally-occurring" amyloid fibrils because it is a transmembrane protein. However, the formation of amyloid fibrils *in vivo* is characteristic of a failure in the normal protein folding process. When a protein misfolds, amyloid fibrils may be formed. The "normal" function or location of that protein has no bearing on its potential to form amyloid fibrils.

For example, the fact that, if it is folded and processed normally, a protein would have a final location in a plasma membrane does not mean that it could not potentially fold incorrectly and form amyloid fibrils. As explained in Jarrett et al., β protein itself is believed to be derived from the putative transmembrane region of βAPP. By the Office Action's reasoning, β protein would not be expected to be capable of forming amyloid fibrils *in vivo*. In fact, the amyloid

deposits formed from β protein are characteristic of Alzheimer's disease.

§ 102 - Kedar et al. Reference

The present invention is directed to processes which result in the production of amyloid fibrils which do not occur naturally. That is, the present invention explicitly does not encompass the natural formation of amyloid fibrils *in vivo*, or the formation of the same fibrils by other means, for example methods of forming *in vitro* the same fibrils which can be formed naturally *in vivo*.

This is different from what is disclosed in Kedar et al. Kedar et al. describes the *in vitro* synthesis of amyloid fibrils from specific hormones, including calcitonin and insulin. Both of these hormones are known to form amyloid fibrils *in vivo*. In particular, calcitonin is the sole constituent of the amyloid deposits associated with medullary thyroid carcinoma, and amyloid deposits of insulin are associated with injection-localized amyloidosis.

This prior art reference thus merely describes the formation of fibrils by a non-natural method, but the fibrils that are actually produced are the same as amyloid fibrils which would form *in vivo*. The methods described in these documents do not, therefore, fall within the scope of the claims now presented.

At the time that document was published (1972), the exact composition of *in vivo* amyloid fibrils had not yet even been determined. It is clear from the introductory section of Kedar et al., at page 1137, that the intention here was to investigate those hormones believed to be involved in localized amyloidosis in endocrine tissues. Kedar et al. clearly only envisages an investigation of those peptides that produce amyloid fibrils *in vivo*. There is no suggestion in this document that amyloid fibrils could be produced using any unrelated peptides. In particular, there is no suggestion in

this document that amyloid fibrils could be produced using peptides that do not form naturally occurring amyloid fibrils *in vivo*.

Claim 40 Amendments

Claim 40 has been further amended to correct the Markush format and grammar.

Extension Petition

An extension petition is also enclosed to extend the time to reply from May 4, 2005 through June 4, 2005, together with a fee authorization.

Conclusion

In view of the above amendment and remarks, reconsideration and allowance are respectfully requested with respect to amended claims 38-47, 49, 50 and 55-60, and new claim 61. Apart from the one month extension fee authorized by the enclosed petition, no additional fees are believed to be needed for the consideration of this submission. In this regard, while there is one new dependent claim, claim 54 has now been canceled, such that the number of dependent claims remains that already paid for. However, if any other fees are required for full consideration of this amendment, please charge them to Deposit Account 17-0055.

Respectfully submitted,

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Dated: May 27, 2005 By: _____

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